

Acute Sporadic Hepatitis in the Republic of Yemen

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The causes of acute icteric viral hepatitis were determined in 78 adult Yemeni patients. Acute hepatitis B (IgM anti-HBc positive) was the most common type (26.9%). Acute hepatitis E (IgM anti-HEV positive) occurred in 14% and was not associated with travel outside Yemen. Sixty per cent of all 78 patients were positive for IgG anti-HEV as were 40% of a series of 48 healthy male blood donors and pregnant females, indicating that HEV is prevalent in Yemen. Acute hepatitis A (IgM anti-HAV positive) and hepatitis C and D were responsible for 5.1%, 6.4%, and 2.6% cases, respectively. This totals to 106%, as an infection with two viruses occurred in 6.4% cases. In 51.3% of all cases, no virological markers of acute hepatitis were detected, suggesting an as yet undiscovered agent. *J Med Virol* 51:64–66, 1997.

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INTRODUCTION

The incidence of acute viral hepatitis (AVH) varies greatly in different geographical areas, being low in North America and Western Europe but high in parts of Africa and Asia including the Middle East. Five major viral forms of acute hepatitis have now been clearly distinguished (types A, B, C, D, and E), and there is growing evidence of additional as yet unidentified viruses [Alter and Bradley, 1995]. The relative importance of these different viruses varies greatly in different parts of the world. For instance, in the United States hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) account for more than 90% of cases [Alter and Mast, 1994], whereas in the Indian subcontinent hepatitis E virus is a major cause [Khuroo et al., 1994].

Acute and chronic viral liver diseases are an important cause of illness in the Republic of Yemen. We have previously published data on the prevalence of

hepatitis B, C, and D serological markers in healthy individuals and patients with chronic liver disease [El-Guneid et al., 1993]. The purpose of this study was to document the viral causes of acute liver disease in Yemen.

PATIENTS AND METHODS

Serum samples were collected from 78 patients aged at least 13 years in the acute phase of viral hepatitis. The diagnosis was based on a typical clinical picture with visible jaundice of less than 4 weeks duration and compatible liver function tests with aminotransferase levels at least 2½ times the upper limit of normal. No patient had a history or physical signs of chronic liver disease, and there was no evidence of excess alcohol consumption or other cause of acute liver injury.

Serum specimens were stored at –20°C.

In the great majority of cases an abdominal ultrasound was carried out which excluded extrahepatic obstructive jaundice. Unfortunately, clinical follow-up of most patients was impossible as they lived in remote rural areas.

Serology for hepatitis E was also carried out on stored serum samples from 24 healthy blood donors and 24 pregnant woman described previously [El-Guneid et al., 1993].

All sera from patients with acute viral hepatitis were tested for IgM antibody to HAV (BIO-KIT, Barcelona, Spain), hepatitis B surface antigen using an enzyme-linked immunoassay technique (BIO-KIT) and confirmed by Abbott HBsAg IMx microparticle EIA, and hepatitis B core antibody by competitive immunoassay (BIO-KIT). Samples negative for hepatitis B surface antigen were tested for hepatitis B surface antibody by a direct immunoassay sandwich technique (BIO-KIT). Hepatitis B surface antigen-positive samples were tested for IgM antibodies to hepatitis B core (Anti-HBc) using Abbott IMx microparticle EIA.

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The HBsAg-positive sera were also tested for anti-delta antibodies by a competitive enzyme immunoassay for the qualitative determination of total antibody to delta antigen (Abbott anti-delta EIA). Hepatitis C antibodies (anti-HCV) were tested for by an enzyme immunoassay (Ortho Diagnostics). IgG antibodies to hepatitis E were tested for in all sera using a qualitative enzyme immunoassay (Abbott Diagnostics). Forty serum samples testing positive for IgG antibodies were subsequently tested for IgM antibodies using HEV IgM Elisa (Gene-labs Diagnostics).

DIAGNOSTIC CRITERIA

Acute hepatitis A was diagnosed if the serum sample was positive for IgM anti-HAV. Acute hepatitis B was diagnosed if the serum was positive for IgM anti-HBc and HBsAg. Patients with HBsAg and anti-HDV who were negative for IgM anti-HBc were diagnosed as having hepatitis D super-infection. Hepatitis C was diagnosed if serum was positive for anti-HCV. Acute hepatitis E was diagnosed if the serum was positive for IgM anti-HEV, and the presence of IgG anti-HEV alone was taken as evidence of prior HEV infection. Where there was no evidence of recent infection with HAV, HBV, HCV, HDV, or HEV the case was classified as acute non-A-E hepatitis. Tests for CMV and EBV were not undertaken.

RESULTS

Of the 78 patients with acute viral hepatitis, only 38 cases (48.7%) were attributable to one or more of the five recognised viral causes of acute hepatitis. Five patients (6.4%) had evidence of infection with two different hepatitis viruses. Hepatitis B virus was the most frequent causative agent and accounted for 21 cases (26.9%), followed by HEV, which accounted for 11 cases (14%). However, in 40 of 78 cases (51.3%), there were no virological markers, and these cases have been classified as non-A-E hepatitis.

Hepatitis A

There were four patients with a mean age of 20 years. One of these patients was also infected with HEV (IgM anti-HEV positive).

Hepatitis B

There were 18 cases with acute hepatitis B only two further cases with the addition of hepatitis C, and a single case also positive for IgM anti-HEV. The mean age of these 21 cases was 33 years; there were 14 males and seven females.

Hepatitis C

There were five males with mean age 41 years. Two cases had hepatitis C antibodies only, two patients also had acute hepatitis B, and one other had acute hepatitis E.

Hepatitis D

There were two cases of hepatitis D super-infection of hepatitis B carriers.

Hepatitis E

There were eight patients with acute hepatitis E, one of whom was also a hepatitis B carrier (HBsAg positive but IgM anti-HBc negative). Three additional patients had a dual infection, one each with HAV, HBV, and HCV. Overall there were nine males and two females with a mean age of 30 years.

There were 47 patients who originally tested positive for IgG anti-HEV. Forty of these sera were tested for IgM antibodies. Only 11 of these 33 with a cut-off index (COI) in the IgG test greater than 2.0 were found to be IgM anti-HEV positive, and these patients are described above as cases of acute hepatitis E. All seven patients who had a COI greater than 1 and less than 2 were negative for IgM anti-HEV.

Non A-E Hepatitis

There were 40 patients (51.3%) in whom there was no identifiable cause of acute hepatic damage. Five were thought to be coincidental HBV carriers (HBsAg positive but IgM anti-HBc and anti-HDV negative).

BLOOD DONORS AND PREGNANT WOMEN

Eight of the 24 blood donors were positive for IgG anti-HEV (33.3%) and in two the COI was greater than 2.0. All eight cases were negative for IgM anti-HEV.

Eleven of the 24 pregnant females (45.8%) were positive for IgG anti-HEV. Seven with COI greater than 1 and less than 2 were tested for IgM anti-HEV and found to be negative.

DISCUSSION

We have shown that sporadic acute viral hepatitis in Yemen is caused by all five of the recognised hepatitis viruses. However, in contrast to the epidemiological pattern in the developed countries, this study highlights the importance of HBV, HEV, and hepatitis non-A-E.

Hepatitis A was responsible for only four cases (5.13%), each of which was in a young adult. In common with most developing countries, hepatitis A is an infection of childhood, and almost 100% of adults in Yemen have naturally acquired immunity [Scott et al., 1990]. However, as living conditions improve, the next generation may be expected to be increasingly susceptible, and acute hepatitis A in adults may become more common unless a vaccination policy is implemented.

Hepatitis B was the most commonly identified cause (26.9% cases). The mode of transmission in Yemen [Murray-Lyon, 1993] is not clear and needs to be urgently addressed. Certainly none of the 21 cases had been transfused. The HBV carriage rate in Yemen is high, and the two published surveys give overall figures in apparently healthy adults of 12.7% and 18.5% [Scott et al., 1990; El-Guneid et al., 1993].

The distinction between acute and chronic hepatitis C is difficult unless follow-up sera are available. Certainly

using the third-generation hepatitis C test, the great majority of patients positive for antibodies are also positive for viral RNA and therefore truly infected. Antibodies to HCV were found in only five patients (6.4%), and two of these had concurrent acute hepatitis B and one acute hepatitis E. It is impossible from our data to know whether these were acute hepatitis C infections or super-infection of an HCV carrier. The prevalence of antibodies to HCV in apparently healthy adults in Yemen was found to be 2.6% and 2.1% in the two published studies [Scott et al., 1992; El-Guneid et al., 1993].

Only two patients had hepatitis D (2.6%). Hepatitis D is uncommon in Yemen compared to some other parts of the Middle East. In the survey by Scott et al. [1990] delta antibodies were found in only two (1.8%) of 112 HBsAg-positive sera, and in our own series we found only two positive sera in 100 (2%) [El-Guneid et al., 1993].

Hepatitis E was responsible for at least 14% of cases of sporadic hepatitis. Unlike other recent studies from the Arabian Peninsula which emphasized the frequent association of acute hepatitis E with recent travel to the Indian subcontinent [Koshy et al., 1994; Shidrawi et al., 1994; Ghabrah et al., 1995], this was certainly not the case with the predominantly poor and solely indigenous Yemeni population which makes up this study. Certainly in other neighbouring countries hepatitis E is endemic [Tsega et al., 1992; Kamel et al., 1995], and the principal mode of spread is thought to be faecal contamination of the water supply [Skidmore, 1995]. Our results from this series of patients with acute viral hepatitis suggest that HEV is widely present in Yemen. Of the 78 patients 47 (60%) were positive for IgG antibodies to HEV. Of these 47, 38 had a high COI (greater than 2.0). Thirty-three of these 38 patients were tested for IgM antibodies, and only 11 were positive. Only these patients were considered to have acute hepatitis E. The other 22 with a high COI in the IgG anti-HEV test had probably been exposed recently. Some of the other five patients (in whom no sera remained for IgM anti-HEV testing) may have been cases of acute hepatitis E, and in addition some authors claim that the IgM anti-HEV response may not always be detected in acute hepatitis E [Khuroo et al., 1994], due either to an inadequate response or to lack of sensitivity of present assays. Furthermore, we found a high prevalence (40%) of IgG antibodies in a population of 48 healthy individuals (blood donors and pregnant woman), further suggesting that the virus is widely prevalent in Yemen. A similar high background level of exposure is reported from India [Arankalle et al., 1995].

In more than half the cases of acute viral hepatitis in this series (51.3%) no detectable viral cause could be found. We did not test for cytomegalovirus or Epstein-Barr virus, but these are unlikely to have been significant contributory causes. We may not have detected some cases of acute hepatitis C in the window period before antibodies develop, and a few cases of hepatitis E may have had no detectable IgM anti-HEV. It seems likely, however, that in a significant number of cases there was at least one as yet unidentified virus. Similar suggestions had been made in other series of patients

with AVH from countries in Africa and Asia. Non A-E hepatitis made up 13% of recent well-documented series of cases from Saudi Arabia [Ghabrah et al., 1995], 28% of cases in Kuwait [Koshy et al., 1994], 19% in Taiwan [Tsai et al., 1994], and 39% in Ethiopia [Tsega et al., 1992]. Even in a well-characterised series of 314 patients with acute hepatitis in Spain [Buti et al., 1994] 18.8% of cases defied the current classification. One such putative virus may be enterically transmitted [Mast and Purdy, 1995], and the newly discovered GB viruses [Zuckerman, 1996] are other candidates.

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